REMARKS

No claims are amended. The disposition of the claims is set forth below:

Disposition of Claims

4)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *20,49,51,57,59 and 65-71* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Claims 1-19, 21-48, 50, 52-56, 58, and 60-64 are Canceled.

New Claim Rejections under 36 U.S.C. Section 103

In the nonfinal office action of September 02, 2010, the Examiner stated :

> Claims 20, 49, 51, 57, 59, 65-70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosen et al (US patent application no 20020187948, dated 12/12/2002, 06/06/2001, IDS) or Rosen et al (WO 02/098286 , dated 12/12/2001, IDS), Lee et al (Molecular Therapy, 2001, 857–866, IDS) and Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, IDS).

Applicants submit herewith the Declaration of Michael R. Rosen stating that he is a co-inventor of the inventions disclosed in US Patent Application 09/875,388, 200201879481, filed on 6/6/2001, Rosen et al., and in WO 02/098286, entitled Implantation of Biological Pacemaker that is Molecularly Determined. He delcares that any invention disclosed but not claimed in Rosen, et al., US Patent Application 09/875,388 and in WO 02/098286, was derived from me and is thus not an invention "by another" with respect to Rosen et al., US Patent Application 10/757,827. Therefore Applicants respectfully submit that the above rejection is moot.

The Examiner also stated:

> Claims 20, 49, 51, 57, 59, 65-70 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Feld et al (US patent no 7294333, dated 11/13/2007, filed on 10/20/2000), Lee et al (Molecular Therapy, 2001, 857-866, IDS, hereafter Lee 1), Lee et al. (USP 7,494,644, dated 2/24/2009, effective filing date 11/7/2002, art of record, hereafter Lee 2), and Qu et al (Circulation res. 2001, 89:e8-14, IDS).

Applicants respectfully disagree.

In the present invention, undifferentiated human Mesenchymal Stem cells (hMSCs) are implanted in the heart, where they form gap junctions with myocardial cells. By definition mesenchymal stem cells, even adult hMSCs, are multipotent, meaning that they are undifferentiated and they can differentiate into a variety of differentiated cell types. Applicants were the first to discover that undifferentiated MSCs are able to form functional low resistance junctions with cardiomyocytes, and naturally couple to heart cells *in situ* via gap junctions that permit dye transfer between stem cells and cardiomyocytes. This is described *inter alia* below:

> [0023] FIG. 3A-C: coupling and ionic and dye transfer between stem cells and between a stem cell and a canine cardiomyocyte (ventricle). A: light micrograph and fluorescence images of dye transfer between stem cells. B: light micrograph and fluorescence images of dye transfer between a stem cell and a canine cardiomyocyte. C: graph representing ionic transfer between a stem cell and canine cardiomyocyte.
>
> [0201] . . . FIG. 2 shows transfer of dye from a stem cell to a HeLa cell. The LY has been delivered to the HeLa cell, presumably by diffusion through gap junctions.

Note that while the hMSCs in the pending claims are transfected to overexpress an ion channel (HCN), they are not engineered to overexpress connexins as is **required** in Lee. Applicants have also described the ability of undifferentiated hMSCs to form gap junctions with cardiomyocytes *in situ* using immunostaining Circ Res 2004; 94:952-959; and they showed that hMSCs express Cx40 and Cx43 using immunostaining Valianus J Physiol. 555.3, 2004 p 617. Copies are attached.

By contrast Feld, cited by the Examiner, describes using only differentiated fibroblasts from the NIH 3T3 cell line that were transfected with ion channel coding sequences and co-cultured with

cardiomyocytes. It was necessary for Feld to use differentiated fibroblasts because undifferentiated fibroblasts are carcinogenic and would cause tumors. Feld states at Col 14, lines 29-36:

> Numerous cell types can be utilized to accomplish such a task, provided the cells possess functional gap junctions and functional ion channels. . . .Examples of suitable cell types include, but are not limited to, fibroblasts, skeletal myoblasts (satellite cells), endothelial cells and the like which can be of autogenic, allogenic, or xenogenic origin.

Feld emphasizes that the implanted cells needed to possess functional gap junctions and ion channels. As the Examiner acknowledges, Feld did not teach the use of stem cells, presumably because at the time stem cells were believed to be unable to form gap junctions.

Regarding Lee, the Examiner states:

> Lee et al (1) provide motivation to use MSC as gene delivery vehicle for treating various conditions. Lee et al teach an ex vivo culture and expansion capabilities and multi potential nature of hMSCs to make hMSCs an attractive cellular vehicle for gene delivery applications. Lee et al show genetically transduced MSCs expanded in culture and maintain the stem cell phenotype and stable transgene expression for over 6 months (see page 858, col. 1, para. 1), but differ from claimed invention by not disclosing injecting MSC to heart or cardiac cell.

The Lee application claims the benefit of U.S. provisional application Ser. No. 60/337,352, filed Nov. 8, 2001. It should be noted that Lee lists mesenchymal stem cells as useful recombinant mammalian cells for implantation; but provides no data and no details regarding their use. At the time the Lee application was filed, it was believed that stem cells and fibroblasts could not form gap junctions. Lee admits this in his description of his invention as follows:

> [0013] The invention provides methods for establishing electrical coupling between cardiomyocytes and recombinant cells which have been genetically engineered to express a connexin protein such as connexin 43 (Cx43) protein. The invention is based on the discovery that genetic modification of skeletal muscle cells to express a recombinant connexin, enables the genetically modified cells to establish electrocommunication with cardiac cells via gap junctions. The recombinant connexin-expressing cells can be used for repair of cardiac tissue and for treatment of cardiac disease by transplantation into cardiac tissue.

Thus Lee teaches that MSCs and fibroblasts must be genetically engineered to overexpress connexins such as Cx43, in order to acquire the ability to form gap junctions, thus enabling them

to functionally couple with cardiomyocytes. Connexin 43 (Cx43) is the major gap junction protein in the ventricular myocardium. Lee's requirement that the implanted MSCs and fibroblasts overexpress recombinant connexins, such as Cx43, in order to be able to form gap junctions with myocardial cells teaches away from the present invention which does not involve engineering the MSCs to overexpress connexins.

Applicants therefore submit that the pending claims are not obvious over the teachings of Lee which requires that the MSCs that overexpress connexins (either alone or in combination with Feld and Qu). In sharp contrast to Lee, the inventors of the present application discovered that undifferentiated hMSCs are able to form gap junctions without being genetically modified to overexpress connexins. See above. The hMSCs in the pending claims are genetically modified with HCN ion channels to generate a pacemaker current, but unlike Lee the hMSCs are not engineered to overexpress connexins.

Applicants respectfully submit that the deficiencies of Feld and Lee are not cured by Qu, and for the reasons stated above, the pending claims are not obvious over the combination of Feld, Lee and Qu.

Therefore, Applicants respectfully submit that the present application is in condition for allowance. Favorable consideration is respectfully requested. If any unresolved issues remain, it is respectfully requested that the Examiner telephone the undersigned attorney at (703) 622-6528 so that such issues may be resolved as expeditiously as possible.

To the extent necessary, a petition for an extension of time under 37 C.F.R. § 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 504213 and please credit any excess fees to such deposit account.

Respectfully Submitted,

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Date

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